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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/369,992	08/06/1999	ANNA KATE URSULA KARA	64-99	7524

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 10/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/369,992	KARA ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-46 have been canceled.

New claims 47-58 have been submitted.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 7, 2004 has been entered.

Please Note: The newly submitted independent claim 47 is being read to be directed to a method that comprises two methods steps, specifically:

Contacting a nucleic acid probe with a sample or
A nucleic acid primer with a sample or
A nucleic acid extracted, purified or amplified from said sample
Under conditions sufficient for hybridization to occur , and
Detecting said hybridization using detection means.

Claim Objections

2. Claim 47 is objected to because of the following informalities:

Claim 47 recites multiple alternative embodiments within a single claim, but how the various alternative embodiments interface is confusing in light of the term "or" is recited in such a way that what parts of the claim go with other parts is not clearly set forth. The phrase "A nucleic acid extracted, purified or amplified from said sample" is not contacted with anything other than the detection means. How can hybridization occur during the contacting step with the extracted, purified or amplified sample, when nothing

has been combined with the extracted or purified or amplified sample nucleic acid to afford hybridization. Additionally it is not clear what is used to amplify the nucleic acid in the sample prior to hybridization, as no structural characteristics are defined or provided for the amplification reagent. Function does not define a specific chemical structure when a reference nucleic acid sequence is not recited.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 47-52 are rejected, as previously applied to claims 1, 5-11,13-15 and 46 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The lack of written description is Not being applied against the recited specific probes and primer, but only the extracted, purified or amplified sample that is only functionally defined the hybridize with a functionally defined detection means.

5. The rejections made of record in paper number 32 (dated August 5, 2003), paragraphs 20-21 and paper number 29, (dated December 16, 2002), paragraph 7 are

incorporated herein by reference (and are provided as attachments to the instant Office Action) in so far as the address the utilization of a nucleic acid derived from any biological sample for hybridization to any detection means that is only functionally defined in the instant claims.

The claims recite the utilization of an extracted, purified or amplified nucleic acid of any size or sequence which is contacted with a functionally defined detection means for detecting the presence of a Plasmodium malarial agent in a biological sample.

The detection means is comprises a sequence of any number of nucleotides in length, and may be of any sequence that will detect any Plasmodial malarial agent that is be known to share some homology (P.falciparum) or less homology (P.vivax) with P.berghei (see McCutchan et al (1984, reference cited herein, page 809, abstract, top of page "The DNA of Plasmodium vivax, which is also a human parasite, fits into a distinctly different group" from that of P.falciparum and rodent malarial parasite P.berghei.)

As the detection means and extracted, purified or amplified nucleotide sequence is not structurally defined other than by functional language, the number of nucleotides that defines the conserved portion of the recited detection mean or hybridization agent that is not positively recited in the claim relative to the extracted, purified or amplified nucleic acid of the sample, could be one or more nucleotides in length. The method utilizes a genus of nucleic acid molecules that may only contain a common nucleotide and is any is able to hybridize to a sequence in a sample or a nucleic acid derived therefrom. The genus of hybridization reagents utilized in the claimed method have not been described to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed.

Applicants have not described, nor disclosed the claimed genus of methods that utilize the recited genus of complementary sequences which meet the functional limitations of being able to detect a human malarial agent.

The specification does not provide written description support for the recited genus of probes and primer sequences in the instant specification. The skilled artisan cannot envision all the contemplated nucleotide sequences by the detailed chemical structure of the claimed polynucleotides and therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Furthermore, In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a

nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The specification fails to provide adequate written description for the claimed genus of probes and primers that share a conserved sequence with SEQ ID NO 1, nucleotides 1147-1740 or with any portion of any extrachromosomal genetic element of P.berghei. The specification does not disclose a representative number of species described by structure, physical or chemical characteristics, function correlated with structure or a combination of these sufficient to establish that the applicant had possession of the genus probes and primers that would detect any human malarial agent and could be used in the claimed method to detect a human malarial agent.

A probe or primer sequence of SEQ ID No 1, nucleotides 1147-1740 does evidence support in the instant specification but not the full breadth of the claims meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Interim Guidelines on Written Description,.(Fed Reg , June 15, 1998, Volume 63, Number 114, pages 32639-32645) and the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

New claims 47-52 contact a sample that has been extracted, purified or amplified with a detection means, but what the source of the biological sample is not so claimed to set forth what nucleic acid has been extracted, purified or amplified.

Additionally, the reagent or reagents used to amplify the biological sample's nucleic acid are not claimed, nor disclosed in the instant Specification, in such a way to show that Applicant has possession of a genus of reagents that can detect any extracted, purified or amplified Plasmodial malarial agent in any type of biological sample when the nucleic acid has not been described by structure correlated with function. The nucleic acid in the extracted, purified or amplified biological sample must evidence hybridization with any detection means that has not been structurally claimed and the hybridization must differentially detect a Plasmodial malarial agent from other nucleic acids that may or may not be in the biological sample, wherein the biological sample is obtained at some future date.

6. In view of the fact that the genus of claimed methods that utilize any nucleic acids that have been extracted, purified or amplified and only functionally defined to hybridize with any functionally defined detection means have not been so described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), that Applicant had possession of the claimed invention and therefore has not enabled the full scope of the what is now claimed, based upon a lack of written description of a highly variable genus of nucleic acid molecules (see Rich et al (Parsitology Today, 2000) teaches populations "exhibit high levels of genetic polymorphism") present in Plasmodial malarial agents.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 47, 51 and 56 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 47 detects a nucleic acid extracted from the sample. In light of the fact that the sample has been only defined to be a biological sample that may or may not contain Plasmodium malarial agent, what is the nucleic acid that was extracted? Is the extracted nucleic acid bacterial cell or mammalian host cell nucleic acid molecules? What is in the extract? Claim 47 detects hybridization of the nucleic acid extracted, purified or amplified from a sample, but no hybridization agent has added to the extracted purified or amplified sample. Essential reagents and methods steps are missing from the claim.

Claim 47 encompasses the utilization of a sample nucleic acid that has been purified or amplified from the sample. The probe and primer recited in claim 47 are not required for amplification of the extracted, or purified or amplified sample, and are not used in the hybridization condition with the extracted, purified or amplified sample as now claimed, based upon the recitation of multiple alternative embodiments "or". What is used to amplify the nucleic acid in the sample? What reagent is used as a differential detection means to distinguish a Plasmodium nucleic acid sequence from a nucleic acid from any cell or random source present in the biological sample? While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations

from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed.

Claim 51 recites the phrase "the detection means used to detect the hybridization comprises identifying a signal"; a methods step does not structurally define the recited detection means. This rejection could be obviated by amending the claim to recite just the reporter molecule bound to ....., or to recite ---wherein the detecting comprises the step of---.

Claim 56 recites the phrase "or an extracted or purified fraction thereof" and refers back to either the sample or blood which are both extractable and purified. Clarification of what is extracted or purified is requested. If the blood is extracted or purified, the rejection could be obviated by amending the claim to recite the phrase ---of said blood--- .

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 47-56 are rejected, (as previously applied to claims 1, 5-14, in paper number 32 and claims 1, 3-4, 8-9, 10 and 13 in paper number 29, which are incorporated herein by reference) under 35 U.S.C. 102(b) as being anticipated by Gardner et al (1993).

Please Note: In light of the P.berghei conserved sequence being any 15 consecutive nucleic acids of SEQ ID No 1, nucleotides 1147 to 1740, the following rejection is being made of record as Gardner et al disclose a highly conserved, LSU rRNA Plasmodium nucleotide sequence that shares 100% sequence identity over 117 consecutive nucleic acids (see sequence alignment attached hereto, the complement of which was incorporated into a primer for the detecting of a human malarial agent in a biological sample.

Gardner et al disclose the claimed invention directed to a method of detecting a human Plasmodium malarial agent in a biological sample, the method comprising the steps of:

contacting a biological sample with a probe or primer (see DNA analysis section, page 1067, col. 2; page 1070, col. 1, first three lines define the most conserved positions and Table 1, col. 2; Figure 4) that comprises a LSU rRNA nucleic acid sequence of SEQ ID NO 1, nucleotides 1147-1740 that is conserved (complementary to "A/U", see page 1068, col. 1, paragraph 3) and found in an extrachromosomal element circular DNA that is a plastid (see sequence alignment) of a human malarial agent, wherein the probe or primer hybridized to DNA from a human malarial agent in the sample (see Figure 4, page 1070); to permit

detecting hybridization (see page 1070, figure 4), wherein the probe was at least 15 nucleotides in length (see page 1067, materials and methods, DNA analysis section and sequence alignment for X61660 and Figure 4, image and narrative).

The reference does not identify the sequence as being from P.berghei, but Gardner et al at page 1068, col. 1, paragraph 3, middle of paragraph, discloses a highly

conserved sequence of P.falciparum, "A/U". The extremely conserved sequence was disclosed, and the complement thereof was incorporated into a primer for detecting a Plasmodial malarial agent of human in a biological sample and the primer comprised a highly conserved sequence for P.berghei (see sequence alignment of X61660). The primer hybridized with a complementary sequence T/A (see primers disclosed on page 1067, col. 2, paragraph 1). The primer detected the presence of human Plasmodial agent P.falciparum DNA in a biological sample.

The biological sample of Gardner was a parasitized erythrocyte sample (see page 1068, col. 1, Transcript analysis, paragraph 5).

The probe or primer was derived from the LSU rRNA (see page 1068, col. 1, paragraph 5 "an oligonucleotide complementary to sequence near the 5' end of the LSU rRNA" and " The complete DNA sequence of the LSU gene is deposited in the EMBL database under the accession number X61660", col. 1, paragraph 4).

The detection was by RNA PCR (see page 1068, col. 1, paragraphs 3-5); specific portions of the LSU rRNA genes were made (see Table 1, page 1070, col.1-2, especially, col. 1, first three lines define the most conserved positions and Table 1, col. 2; Figure 4) that comprises a LSU rRNA nucleic acid sequence of SEQ ID NO 1, nucleotides 1147-1740 that is conserved (complementary to "A/U", see page 1068, col. 1, paragraph 3) and found in an extrachromosomal element circular DNA that is a plastid (see sequence alignment) of a human malarial agent, wherein the probe or primer hybridized to DNA from a human malarial agent in the sample (see Figure 4, page 1070); to permit detecting hybridization (see page 1070, figure 4), wherein the probe was at least 15 nucleotides in

length (see page 1067, materials and methods, DNA analysis section and sequence alignment for X61660 and Figure 4, image and narrative).

The hybridization conditions for RNA analysis were disclosed in light of references 7 & 8 (see page 1067, col. 2, paragraph 2, lines 1-2; Gardner et al 1991, Molecular and Biochemical Parasitology, Vol. 48, (reference of record) define a plurality of hybridization conditions, see page 78, col. 2, paragraphs 2-3 and col. 1-2 of page 79, the conditions being low, medium and high stringency conditions).

Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states "Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. "The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art".

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 57-58 rejected under 35 U.S.C. 103(a) as being unpatentable over Gardner et al (1993, Nucleic acid Research, reference of record) in view of Obst et al (1990, Histochemistry, reference of record).

Gardner et al teach and show a method of detecting a human Plasmodium malarial agent in a biological sample, the method comprising the steps of:

contacting a blood derived (erythrocyte) biological sample with a probe or primer (see DNA analysis section, page 1067, col. 2; page 1070, col. 1, first three lines define the most conserved positions and Table 1, col. 2; Figure 4) that comprises a LSU rRNA nucleic acid sequence of SEQ ID NO 1, nucleotides 1147-1740 that is conserved (complementary to "A/U", see page 1068, col. 1, paragraph 3) and found in an extrachromosomal element circular DNA that is a plastid (see sequence alignment) of a human malarial agent, wherein the probe or primer hybridized to DNA from a human malarial agent in the sample (see Figure 4, page 1070); to permit

detecting hybridization (see page 1070, figure 4), wherein the probe was at least 15 nucleotides in length (see page 1067, materials and methods, DNA analysis section and sequence alignment for X61660 and Figure 4, image and narrative).

Gardner et al (page 1068, col. 1, paragraph 3, middle of paragraph), teaches a highly conserved sequence of P.falciparum, the complement thereof was incorporated into a primer for detecting a Plasmodial malarial agent of human in a biological sample and the primer comprised a highly conserved sequence for P.berghei (see sequence alignment of X61660), and utilized a detectable signal for the detecting of hybridization but differs from the instantly claimed invention by failing to show the signal to be

generated by a non-isotopic reporter molecule biotin, and the biological sample to be a dried blood sample.

Obst et al teach a method of detecting a Plasmodium malarial agent in a biological sample, the method comprising the steps of: contacting and detecting hybridization in a dried blood sample (see page 101, col. 2, material and methods, paragraph 2) which utilized a biotin reporter molecule (see page 102, col. 2, paragraph 3; page 103, col. 1-2 Discussion section and all frames of Figure 1) in an analogous art for the purpose of detecting a malarial agent utilizing a non-isotopic reporter molecule which generates a specific signal with high resolution (see page 102, col. 2, paragraph 2, last three lines).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of Gardner et al to include the analysis of dried blood samples and a biotin non-isotopic signal reporter molecule as suggested and taught by Obst et al because both Gardner et al and Obst et al teach methods of detecting a malarial agent in a blood derived biological sample, and Obst et al teaches that dried blood smears are readily used as a biological sample for the detection of a malarial agent, and Obst et al also teaches the advantage of utilizing a biotin non-isotopic reporter molecule for the attainment of enhanced signal generation (see page 102, col. 2, hybridization signal as a function of the probe).

In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of detecting a malarial agent in a dried blood sample utilizing an LSU rRNA biotin report molecule utilizing the probe or primer of Gardner et al with the biotin reporter molecule of Obst et al because

Obst et al teach a non-isotopic reporter molecule biotin defined and provided means for generating a specific signal with high resolution (see page 102, col. 1, paragraph 3, signal detection and col. 2, paragraph 2, last three lines) due do the ability of biotin to specifically interact with a fluorescently labeled anti-biotin antibody system which resulted in a highly amplified the biotin signal reporter molecule of high resolution.

Gardner et al in view of Obst et al obviates the instantly claimed invention.

Conclusion

12. This is a non-final Action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on 7:30-5:00 M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
September 28, 2004

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